REMARKS

Claims 1-15 are pending and claims 1, 8, 12 and 14 have been withdrawn from consideration. Claims 2-7, 9-11, 13 and 15 are rejected on various grounds.

In response, claims 2, 5, 9, 10 and 13 are amended. The term added to claim 2 is supported, for example on page 3, last paragraph, lines 7-9 and on page 12, first paragraph, lines 8-10 of the specification. Grammatical changes to the other claims have been made. Accordingly, no new matter has been added.

Arguments are provided for how each amendment moots or otherwise overcomes certain rejections and objections from the November 25, 2003 office action. Also, a review of the deficiencies of the cited art and how the amended claims are non-obvious over that art is provided.

Reconsideration and allowance in view of the amendments and arguments respectfully are requested.

1. Incorporation by Reference Objection

On page 2 of the office action, the Examiner has objected to a statement on page 5, lines 4-6 of the specification regarding the sufficiency of a reference to information in a filed patent application. The Examiner has invited applicants to submit an amendment that incorporates the cited information into the specification. In response, applicants point out that the description of materials at page 5 lines 4 to 6 have been available to the public and has been known to skilled artisans for 10 years and that a skilled artisan in this field who reads the specification already enjoys such availability. Adding further information already known is not needed to practice the invention under these circumstances.

Reconsideration and removal of this objection courteously is solicited.

2. Informalities Objections

Typographical errors pointed out on page 2 of the office action have been corrected as follows.

The five sequences without SEQ ID numbers mentioned by the Examiner on page 2 of the office action have been labeled with SEQ ID NOs: 12, 13, 14, 15 and 16, respectively. Pages 5 and 17 of the specification and Figure 1 have been amended accordingly.

A new sequence listing in paper and electronic form is being prepared that has the 5 new sequences, and will be sent upon completion.

Claim 2 now recites "comprising from about."

Claim 10 now includes recitation from claim 1, making this claim independent, and the word "of" has been removed.

Claim 10 now depends from claim 1 and recites "a protein encoded by the DNA."

Claim 3 now recites more specifically where sequences are obtained, and is not limited to a single sequence.

3. Rejections under 35 USC § 112

Claims 2 and 5 have been rejected because of the "metes and bounds" of these claims in view of the term "functional." Applicants point out that the function of the zeta chain is described throughout the specification, which a skilled artisan quickly and clearly understands. For example, the specification states on page 3 line 11 that during operation of the three part conjugate (as is claimed), [b]inding of a cell-bound ligand....leads to zeta chain-mediated signal transduction within the CTL, and eventually results in the lysis of the cell carrying the ligand." A skilled artisan very clearly will understand whether a particular construct has this function by, for example, observing whether a cell undergoes lysis. It is clear that the zeta subunit serves "as a signaling component" (page 3 line 16). Even more specific is the description on page 10 lines 15 to 19: "[a] functional zeta domain is a protein which upon expression in T cell hybridomas deficient in TCR....." Still further, a scientifically acceptable assay for determining this functionality is provided on line 19 (S. Frank et al.), which a skilled artisan can follow.

The Examiner explains on page 3, middle, that the recitation of "derivable" in claim 2 means that the claim "can read on structural alterations of said antigen binding domain and zeta chain." Applicants agree with this statement and point out that this is clear to a skilled artisan reader as well. Accordingly, this term is not vague and indefinite. In this context,

applicants point out that the courts have acknowledged the sophistication and relative maturation of molecular biology such that a description can include a functional term, if that term involves known structure, or is coupled with structure in an understandable way, as described by the Court of Appeals for the Federal Circuit in the Enzo case of 2002 see Enzo Biochem, Inc. v. Gen-Probe, Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). More specifically, a first "common features possessed by members of the (claimed DNA) genus that distinguished them from others" is coupled with a second description of "a sufficient number of species within the very broad genus to indicate that the inventors had made a generic invention, i.e. that they had possession of the breadth of the species, as opposed to merely one or two species."

In this case, the two step rule for obtaining broad claim scope to a range of previously unknown sequences is met by the prior art coupled with the specification. That is, the "common features possessed by members of the (claimed DNA) genus that distinguished them from others" is provided by referral to the zeta "chain derivable from the T-cell antigen receptor." As the Examiner pointed out, this class of molecules already is known. Applicant does not need to provide examples that already exist in the art. For the second step, applicants have provided examples as described, for example on page 10, lines 10 to 26. See page ten line 19 to 23, which provide several of the earliest species that now are more than 12 years old. The numerous examples of this species are so well known that this sub-component of the claimed invention is treated as an available item that the skilled reader is expected to go out and select on his own. The claimed invention is not focused on new zeta proteins but instead an innovative combination that has this 12 year old, well known component part within it.

Reconsideration and allowance are requested.

On the 11th line from the bottom of page 2 from the office action, the Examiner suggests the amendment of claim 3 to recite sequences and remove the "laboratory designations only." In response, claim 3 has been amended by adding "is a sequence produced by a hybridoma cell line having a deposit number selected from the group consisting of 90112115, 90112116, 90112117, and 90112118."

Reconsideration and allowance are requested.

The Examiner has rejected claim 5 as "vague and indefinite" as not stating "the origin of the transmembrane and cytoplasmic domains." In response, the term " of the zeta chain" has been added to this claim.

Reconsideration and allowance are requested.

At the bottom of page 3 of the office action, the Examiner rejects claims 9 and 10 on indefiniteness grounds. Applicants have followed the Examiner's suggestion and have added the terms "the DNA of claim 2" and "protein encoded by the DNA of claim 2," respectively. Reconsideration and allowance are requested.

On page 4, the Examiner rejects claim 10 as allegedly lacking "an active method step." In response, applicants have added the phrase " removing bifunctional protein from the host cell culture" to this claim.

Reconsideration and removal of this objection are requested.

Also on page 4, the Examiner has rejected claim 13 for not reciting "any active, positive steps." In response, this claim has been amended to recite positive steps: "contacting the cancer with CTL that expresses the DNA described in claim 2."

Reconsideration and allowance are requested.

4. Rejection under 35 USC § 101

Claim 2 and claims dependent thereon have been rejected on section 101 grounds because host cells and patients may contain the subject matter. In response, applicants point out that the claims do not cover living animals but only a novel biological substance. The claimed material is not a naturally occurring substance that has been found naturally in patients. Applicants point out that practice of the invention may lead to occurrence of claimed non-naturally occurring substances within host cells and patients. This does not negate patentability, however and is a common situation. By way of example, a novel drug,

transgenic protein or metabolite may be made or found within a patient, yet this does not make the material naturally occurring and therefore unpatentable.

Reconsideration and allowance are requested.

5. Rejections under 35 USC § 103

From the bottom of page 4, the Examiner has rejected claims 2-7, 9-11 and 15 on alleged obviousness grounds in view of Capon, combined with Wels and Huse et al. Applicants assert three separate and independent bases for removing this rejection.

i. Applicants point out that a prima facie case of obviousness is lacking because one element of these claims is missing from every cited reference. None of the references describe a hinge region "comprising from about 40 to about 200 amino acids."

Reconsideration and allowance courteously is requested.

ii. Applicants further note that even when a hinge region is mentioned, the hinge is between two portions of a binding site and not between "an antigen binding domain" and "a functional zeta chain." Although this is implicit in the claims, applicants have amended claim 2 to drive home this point, which represents a separate reason for patentability over the cited references. Claim 2 now recites : "; wherein the hinge region couples the antigen binding domain to the functional zeta chain."

Reconsideration and allowance are requested.

iii. Even combinations of sub-portions of the claimed combination (i.e. that lack the missing claim element noted in i) above) cannot be achieved because of lack of motivation.

It appears that the Examiner finds motivation to include or retain hinge regions in a chimeric molecule that might be prepared following the teachings of Wels et al in combination with Capon et al.

This motivation cannot exist, however for the following reasons:

Huse et al teach the generation of combinatorial libraries of Fab fragments by phage lambda. While Huse et al. might teach that monovalent Fab fragments have less affinity for antigen, this is not relevant to functionality of the claimed sub-parts. The hinge region of the claimed sub-parts is used for something entirely different. Any motivation to combine monovalent Fab fragments does not apply to the different non-analogous materials recited in the claims.

In contrast to the apparent assumption of the Examiner that the hinge region recited in claim 2 is included to allow dimer formation with consequent higher affinity, the hinge region instead serves as a positioner allowing the extracellular ligand-binding domain to protrude a certain distance range from the host cell surface.

Accordingly, motivation does not accrue and removal of this rejection courteously is solicited.

Applicants further note that skilled artisans well understand that the zeta chain of the T-cell receptor always exists as a dimer due to formation of a disulfide bridge between two zeta proteins via cysteine residues in the short extracellular part of zeta (which also exists in the zeta fragment as claimed). Therefore, a construct lacking the hinge region also would have been expected to exist as a dimer even as claimed. The inventors have confirmed this point in a scientific peer-reviewed publication (Gene Therapy 2: 539-546, 1995 see Figure 2, right panel), which can be supplied if needed.

Accordingly, the inclusion of an immunoglobulin hinge region into such constructs merely to allow dimer formation of higher affinity binding is not required for formation of such. Consequently, a skilled artisan would not have been motivated to make the combination of Huse with Capon and Wels to get a combination of inserting a hinge region in order to produce dimeric fusion proteins.

Because motivation would be lacking, removal of this rejection courteously is requested.

Regarding combination of the hinge region, the Examiner refers to page 7, lines 18-27 of Capon, which states that the extracellular domain may consist of an Ig heavy chain that may in turn be covalently associated with Ig light chain by virtue of the presence of CH1 and hinge regions, or may become covalently associated with other Ig heavy/light chain complexes through the presence of hinge, CH2 and CH3 domains. The embodiment described in the cited passage of Capon requires that the extracellular domain consist of an Ig heavy chain. Considering the basic structure of IgG, the heavy chain comprises the N-terminal variable region VH followed by the constant region CH1, the hinge region, the constant regions of CH2 and CH3 (VH-CH1-hinge-CH2-CH3). This implies that the hinge region is an internal portion within the primary structure of the heavy chain, yet is an internal portion within the extracellular domain of Capon.

In direct contrast thereto, the hinge region as claimed (after amendment of claim 2) separates the antigen binding portion from the zeta chain (transmembrane and cytoplasmic part).

Applicants further point out that Capon does not teach a hinge region of 40-200 amino acids and that to the extent any hinge region exists in Capon, this is merely part of an extracellular domain. Wels does not teach a hinge region.

Accordingly, reconsideration and removal of this rejection is requested.

Applicants lastly point out that the arguments above are not merely academic but are backed up by real world experience. A construct lacking a hinge region would be non-functional, and therefore not meet the claim recitations. The authors have reported this in Gene Therapy 2: 539-546 1995 (Moritz and Groner), which describes the construction of such a fusion protein lacking a hinge region ("scFv(FRP5):zeta;ErbB2-specific FRP5 fragment as an extracellular domain directly linked without hinge to the zeta chain transmembrane and intracellular domains) and have compared its activity with that of two different embodiments as recited in the claims (ErbB2-specific FRP5 fragment as an extracellular domain linked via an Ig-like hinge region derived from CD8alpha (hinge) or a hinge region derived from CD4 (D3/D4) to the zeta chain transmembrane and intracellular domains). In that study the

authors clearly showed that the construct lacking the hinge region is not functional in T-cells, whereas both embodiments of the claimed invention are fully functional in T-cells. Therefore, a construct resulting from a combination of the teachings of Capon et al. and Wels et al. would not have been functional.

Accordingly, Capon at best suggests the use of CD8alpha and CD4 as extracellular ligand-binding domains, but not the use of the hinge regions of CD8alpha or CD4 without including their ligand-binding activities.

In view of these several reasons, including lack of a claim term and lack of motivation to combine the remaining claim terms, removal of the 103 rejection courteously is solicited.

Reconsideration and allowance are requested.

If a teleconference would be helpful to resolve remaining issues, the examiner is requested to contact the undersigned at 202-912-2195.

Respectfully submitted,

Date: January 30, 2004

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